REMARKS

Claims 1-3, 5 and 6 are currently pending.

Applicants have amended claim 1 to recite that the chimeric protein has improved refolding attributes relative to the naturally occurring superfamily member from which the finger 1 and heel subdomains are derived.

Applicants have amended claim 5 to improve its form by replacing "domain" with "subdomain."

Applicants have amended claim 6 to recite that the dimer has two identical monomers.

None of the amendments adds new matter.

Applicants now address the Examiner's rejection.

THE REJECTION

35 U.S.C. § 103(a): Claims 1-3, 5 and 6

The Examiner has maintained the rejection of claims 1-3, 5 and 6 under 35 U.S.C. § 103(a). The Examiner contends that the claims are unpatentable over Keck et al., U.S. patent 6,040,431 ("Keck") in view of Griffith et al., Proc. Natl. Acad. Sci, 93, pp. 878-883

(1996) ("Griffith"), Luyten et al., WO96/14335 ("Luyten"), Qian et al., Proc. Natl. Acad. Sci, 89, pp. 6290-6294 (1992) ("Qian") and Daopin et al., Science, 257, pp. 369-373 (1992) ("Daopin"). Applicants traverse.

Applicants have amended claim 1 (and claims dependent therefrom) to recite a dimeric chimeric TGF-ß superfamily proteins wherein one monomer comprises a CDMP-2 finger 2 subdomain (residues 68-98 of SEQ ID NO:86) and a finger 1 and heel subdomain from a second member of the superfamily and wherein the chimeric protein has improved refolding attributes relative to the naturally occurring superfamily member from which the finger 1 and heel subdomains are derived. Applicants respectfully submit that amended claims 1-3, 5 and 6 are not obvious over Keck, in combination with Luyten, Griffith, Qian and Daopin.

To support his position that Keck discloses the swapping of subdomains between the various TGF-ß superfamily members, the Examiner points to the statement in Keck that the "sequences for the finger and heel regions may be copied from respective finger and heel regions of any known TGF-ß superfamily member. Alternatively, the finger and heel regions may be

selected from the amino acid sequence of a new member of this superfamily discovered hereafter" (column 4, lines 58-64). Applicants respectfully submit that this statement in no way indicates that the subdomains of the various TGF-ß superfamily members may be swapped. Moreover, the specification at column 10, lines 41-47 describes the difference between the TGF-ß superfamily members and morphons. The specification states that "the morphons are active as a monomer subunit and comprise in the single subunit, two finger regions which normally would belong to one subunit of the natural dimer and a heel region which normally would belong to the other subunit of the natural dimer" (emphasis added; column 10, lines 42-47). The finger 1, finger 2 and heel regions in the proteins disclosed in Keck come from one natural dimer. The only situation that a morphon according to Keck would comprise regions from more than one member of the TGF-ß superfamily is when the natural dimer is a heterodimer. And in that case, the two finger regions are from the same member of the superfamily and the heel region is from another member of the superfamily.

The present invention however, involves the swapping of the finger 2 subdomain such that the finger 2

subdomain is from a different member of the superfamily than are the finger 1 and heel subdomains. Moreover, the chimeric proteins of the present invention have improved refolding attributes relative to the naturally occurring superfamily member from which the finger 1 and heel subdomains are derived. It is the substituting finger 2 (i.e., CDMP-2 finger 2) subdomain which confers the improved refolding attribute to the protein. Therefore, unlike the claims of the instant application, which require that the finger 2 subdomain be from a different member that the finger 1 subdomain, the finger 1 and finger 2 subdomains of the proteins described in Keck are from the same member of the superfamily. Moreover, nothing in Keck teaches or suggests that the finger 2 subdomain of CDMP-2 would confer improved refolding attributes to another member of the TGF-ß superfamily. None of Qian, Griffith, Doapin and Luyten remedy these deficiencies.

Qian discloses a chimera of two TGF-β isoforms (TGF-ß1 and TGF-ß2). The chimeric protein of Qian comprises residues 1-39 of TGF-ß2 (corresponding to residues 1-25 of SEQ ID NO: 41 plus additional N-terminal sequence), followed by residues 40-82 of TGF-ß1

(corresponding to residues 26-68 of SEQ ID NO: 40), followed by residues 83-112 of TGF-ß2 (corresponding to residues 69-98 of SEQ ID NO 41). Therefore, residues 1-39 in Qian correspond to a portion of the finger 1 subdomain as defined in the present application (residues 2-25 of SEQ ID NO: 41) plus additional N-terminal amino acid residues, residues 40-82 in Qian correspond to a portion of the finger 1 subdomain (residues 26-29 of SEQ ID NO: 40) and the heel subdomain up to the fourth residue of the finger 2 subdomain; and residues 83-112 in Qian correspond to most of the finger 2 subdomain (residues 69-98 of SEQ ID NO: 41, missing the first four residues).[1] Therefore, as in the case of Keck, the chimeric proteins described in Qian comprise finger 1 and finger 2 subdomains which are from the same member of the superfamily.

The Examiner contends that Qian provides a reasonable expectation of success and motivation to select CDMP-2 subdomains for the chimera because CDMP-2 has chondrogenic activity in vivo but substantially no

[1] Applicants note that in their October 8, 2003 Reply, they inadvertently misidentified the subdomains of the instant application which correspond to residues 1-39, 40-82 and 83-112 of Qian.

osteogenic activity and an OP-1/CDMP-2 chimera would provide a practical approach to investigate structure function. Applicants respectfully submit that Qian merely discloses that a chimeric TGF-ß molecule such as the one disclosed (TGF-ß2-ß1-ß2) "is a practical approach to investigating the structure/function relationships in closely related proteins." Other than the one specific TGF-ß1/ß2 chimera, Qian does not provide any teaching or suggestion as to any other chimeric molecules and which specific regions are important for the various functions of these proteins. Qian does not provide any suggestion or motivation to replace the finger 2 subdomain of the various TGF-ß superfamily member proteins with a finger 2 subdomain from CDMP-2 as is recited in the claims of the instant application. Nor does Qian teach or suggest that the finger 2 subdomain of CDMP-2 would confer improved refolding attributes to another member of the TGF-ß superfamily. Applicants respectfully submit that based on the teachings of Qian (as well Daopin, Luyten and Griffith, discussed *infra*) in combination with Keck, the skilled worker at the time of the invention would not have had a reasonable expectation that replacing the finger 2 subdomain of a TGF-ß superfamily member protein

with that of CDMP-2 would result in improved refolding of the protein. Therefore, the combination of Keck and Qian (as well Daopin, Luyten and Griffith, discussed *infra*) does not render the claimed invention obvious.

The Examiner contends that Daopin "was included in the rejection to indicate the close structural similarity between TGF-ß2 and other members of the TGF-ß superfamily [ ] and to suggest that the only stable form of TGF-ß2 in solution is a [dimer]." The Examiner further contends that Keck identifies the finger 1, heel and finger 2 regions and teaches making chimeric monomers. The Examiner, therefore, concludes that it would have been obvious to one of skill in the art to make a dimer because of the close structural similarity between TGF-ß2 and other members of the superfamily and the only stable form of TGF-ß2 is a dimer.

Notwithstanding the fact that Daopin teaches that TGF-ß2 is a dimer and shares 66-80% identity with TGF-ß1 and TGF-ß3 through TGF-ß5 and 25-40% sequence identity with other members of the superfamily, the combination of Daopin with Qian and Keck (as well as Luyten and Griffith, discussed *infra*), does not render the claims of the instant application obvious. Nothing

in the combination of these documents provides the motivation to make the specifically claimed chimeric molecules wherein the finger 2 subdomain has been replaced with residues 68-98 of CDMP-2. Moreover, nothing in the combination of Keck, Qian and Daopin (as well as Luyten and Griffith) provides the skilled worker with an expectation that replacing the finger 2 subdomain of a TGF-ß superfamily member protein with the finger 2 subdomain of CDMP-2 would result in a molecule with improved refolding properties as recited in the claims of the instant application.

The Examiner contends that Luyten was included because it discloses the sequence of CDMP-1 and CDMP-2. Applicant acknowledges that Luyten discloses the sequence of CDMP-1 and CDMP-2. Nevertheless, as discussed above, the combination of Luyten, Keck, Qian and Daopin (and Griffith) does not teach or suggest the chimeric molecules as recited in the claims of the instant application. Nor does the combination of these documents provide the skilled worker with a reasonable expectation of successfully making a chimeric protein having improved refolding attributes.

The Examiner contends that Griffith was included "to teach that all of the TGF-ß members share the OP-1/TGF-ß structural motif." Applicant agrees that Griffith discloses that the various members of the TGF-ß superfamily share a structural motif. Nevertheless, the combination of Keck Qian, Daopin, Luyten and Griffith, does not render the claims as recited obvious. The claims of the instant application recite a chimeric protein wherein the finger 2 subdomain of the various members of the superfamily is replaced with that of CDMP-2 and wherein the chimeric protein has improved refolding attributes relative to the naturally occurring superfamily member from which the finger 1 and heel subdomains are derived. Nothing in the combination of Keck, Qian, Daopin, Luyten and Griffith would have motivated the skilled worker to replace the finger 2 subdomain of the various TGF-ß superfamily members with that of CDMP-2 in order to improve the refolding attributes as recited in the amended claims. Moreover, at the time of the invention, the skilled worker would not have had a reasonable expectation that such replacement of the finger 2 subdomain would result in improved refolding.

Accordingly, applicant respectfully requests that the Examiner withdraw this rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and allow the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

Respectfully submitted,

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